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(54) Title: FLAVONOID DRUG AND DOSAGE FORM, ITS PRODUCTION AND USE

(57) Abstract: A medicament, dosage form and food additive for the therapeutic, prophylactic and/or palliative treatment of diseases and health and cosmetic disorders, which comprises a composition containing at least one preferably at least two, flavonoid as the active ingredient. The invention also relates to the use of these products in treatment methods.

Flavonoid drug and dosage form, its production and use

The present invention relates to a flavonoid drug, a flavonoid dosage form, their production and use. The dosage form include products used as food additives or alimentary products.

The flavonoid drug and the flavonoid dosage form of the present invention is useful for the therapeutic, prophylactic and/or palliative treatment of cancer, psoriasis, diabetes, rheumatism, cardiovascular diseases, elevated blood pressure, elevated cholesterol levels, caries, and colds. , in general for the treatment of disorders and disease related to aging.

The drug of the present invention is also useful as medicament for the protection and control of cholesterol and human DNA, RNA, lipids, enzymes, hormones in order to reduce and/or prevent the undesired oxidation thereof and as an antibiotic or cosmetic preparation which composition contains at least one flavonoid as the active ingredient.

In general the preparation of this invention is suitable for the treatment of all kinds of disorders and disease related to aging including medicinal and cosmetic treatment.

The dosage form of the invention especially include food additive products and alimentary products freely sold and having the above mentioned effects.

The dosage form of the present invention is suitable for oral, parenteral or topical administrationand and may be prepared as capsules, powders, tablets, liquids and alike.

Flavonoids are one of the widest found groups of vegetable chemical compounds. They are polyphenolic antioxidants naturally present in vegetables, fruits, and beverages such as tea and wine. More than 3000 flavonoids have been found and identified. All flavonoids have a common biosynthetic origin and they therefore possess the same basic structural

element, namely a 2-phenyl chromane skeleton. Flavonoids occur mainly as glycosides but they may also be in the form of free phenols and sulphates.

Oxidation of low density lipoproteins by free radicals is thought to play a central part in the development of atherosclerosis. Antioxidants may thus delay the onset of atherogenesis. Several flavonoid compounds have been shown to have antioxidant properties in vitro, inhibiting the oxidation of low density lipoproteins and reducing thrombotic tendencies by inhibiting platelet aggregation.

In a big Dutch study Hertog MGL, et al, Lancet 1993; 342:1007-11, showed that regular intake of foodstuffs which naturally contain flavonoids decreased mortality from myocardial infarction by half. The flavonoid content of the diet was calculated on the basis of an intake of tea, onions and apples.

A recent Finnish study by Knekt P, et al, BMJ, 24 February 1996, Vol. 312, p. 478-481, supports the above findings. People eating a lot of apples and onions seem to be better protected from the risk of coronary diseases than those lacking said foodstuffs in their diet. Especially women seem to benefit from a diet rich of flavonoids. The risk of mortality from coronary diseases for the group of women receiving the biggest amount of flavonoids was only half of the risk for the group receiving the smallest amount. For men the difference was 20 per cent. According to the above study, flavonoids posses similar oxidation inhibiting effect on cells as vitamins E and C.

Kaegi, E., Canadian Medical Association Journal, April 21 1999 suggests that the polyphenols of green tea have a chemotherapeutic effect on breast cancer and recommends a moderate intake of green tea. The inhibitive effects of flavonoids on the growth of tumor cells has been mentioned in Svenska Dagbladet on 26 November 1999.

Patent application WO 98/18348 by the same inventor relates to the use of flavonoids as flavoring agents, especially for replacing table salt. A mixture of

the flavonoids of green tea, onion and apple are described as a preferred, flavoring mixture.

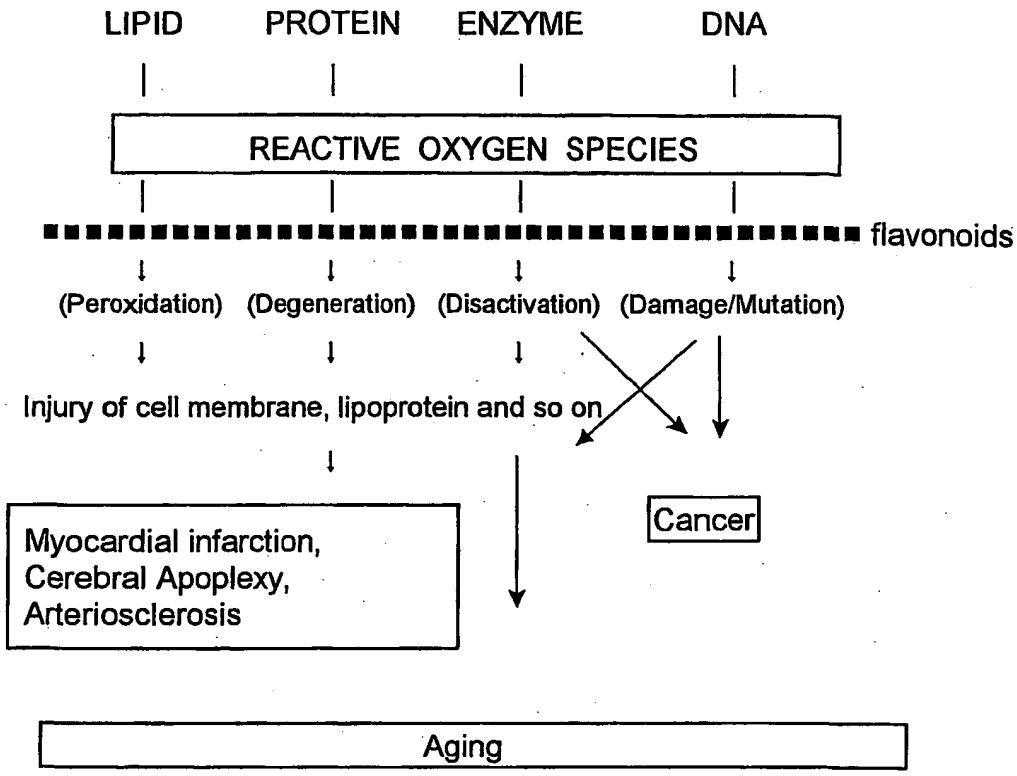
In the prior art the intake of flavonoids was mainly provided by people eating flavonoid-containing fruits and vegetables or drinking flavonoid-rich beverages such as tea and wine.

The present invention is based on the realization that flavonoids may be extracted and/or powdered and made into a drug or dosage form which may be used for the therapeutic, prophylactic and/or palliative treatment of serious disorders such as cancer. The product also potentially has an activity against psoriasis, diabetes and rheumatism. It can reduce blood. pressure and cholesterol levels. It can reduce the risk for stroke and heart diseases. It may also provide protection against influenza. It is potentially useful for combatting disorders caused by stress. It can further successfully be used as an antioxidant for reducing or preventing the undesired oxidation of cholesterol and DNA in humans

The drug and dosage form according to the invention has little or no toxic effects. It can be administered orally, parenterally and/or topically. It has a good human acceptance and low cost of preparation.

The flavonoid drug and the dosage form of the present invention is easy to use and is suitable for both home use and hospital care.

A diagrammatic presentation of the function of flavonoids on some oxidative species:



In the above diagram aging should be interpreted to include not only medicinal disorders but also cosmetic disorders and problems.

The aim of the invention is to prevent (presented by a dotted line in the scheme above) the undesired oxidation of the species.

The present invention is defined in the appended claims.

Thus, the present invention is directed to a medicament and a dosage form for the therapeutic, prophylactic and/or palliative treatment of cancer, psoriasis, diabetes, rheumatism, cardiovascular diseases, elevated blood pressure, elevated cholesterol levels, caries, and colds, which comprises a composition containing at least one flavonoid as the active ingredient.

The present invention is further directed to a medicament for the protection and control of cholesterol and human DNA, RNA, lipids, enzymes, hormones in order to reduce and/or prevent the undesired oxidation thereof and as an

antibiotic or cosmetic preparation which composition contains at least one flavonoid as the active ingredient

The preferred medicament comprises a mixture of at least two, and preferably three flavonoids in an orally, parenterally or topically administrable dosage form.

The preferred flavonoids are selected from flavonoids of onion, green and black tea, apple, grape, bark of Ginko Biloba and Maritime pine. Especially preferred are quercetin and its derivatives, epigallocatechin and its derivatives, especially epigallocatechin-3-gallate, and myricetin. The preferred flavonoid is epigallocatchin gallate. It is most preferably used in combination with quercetin and vitamin C, possibly also vitamin E. Vitamin C is believed to prevent oxidation of polyphenols and to reactivate vitamin E.

The medicament and food additive of the present invention preferably contains querectin and/or its derivatives in an amount of 10 to 30 mg/100 g and epigallocatechin-3-gallate 80 to 200 mg/100 g calculated on the weight of the product.

The dosage form according to the present invention is suitable for the therapeutic, prophylactic and/or palliative treatment of cancer, and it is formulated into a capsule, pill, tablet, cream, ointment, liquid or an injectable fluid which contains at least one flavonoid as the active ingredient. It preferably contains a mixture of at least two, and preferably three flavonoids selected from flavonoids of onion, green and black tea, apple, grape, bark of Ginko Biloba and Maritime pine.

The dosage form according to the invention preferably contains an antioxidant, such as C-vitamin and/or E-vitamin, for preventing polyphenol oxidation from taking place in the preparation.

The dosage form of the present invention can be produced by mixing a powder and/or an extract of onion, green black tea and/or apple and/or grape and/or

extract of fresh bark of Ginko Biloba and/or Maritime pine with at least one pharmaceutically acceptable carrier and formulating it into a dosage form for oral, parenteral or topical administration. An antioxidant such as C-vitamin and/or E-vitamin is preferably included in the formulation.

The drug of the present invention is preferably used for clinical nutrition. It can be easily administered orally in the form of a tablet, pill or capsule or it can be in the form of a liquid or a powder to be dissolved in a liquid. It can be drunk as a juice for thirst or as a table drink. It can also be administered by a tube directly into the stomach. The last mentioned adminstration form is especially suitable for cancer/geriatric and other chronic patients.

The topically administrable creams, lotions and ointments can be used for prophylaxis, palliation and treatment of excessive exposure to UV radiation and/or melanoma. Cosmetic type lotions or shampoos may be used to prevent and cure psoriasis, but also other more cosmetic dermatological disorders may be treated.

The preferred flavonoids are selected from flavonoids of onion, tea and apple, and an especially preferred mixture comprises a mixture containing onion powder (about 35 to 50 %), green and/or black tea extract (about 30 to 40 %), and apple powder (about 20 to 30 %).

Preferred flavonoides may further be selected from flavonoids derived from onion, green tea, apple, grape, Ginko Biloba and Maritime pine as follows: onion powder 20 to 50 %, tea extract 10 to 40 %, apple powder 10 to 30 %, grape powder 10 to 40 %, Ginko Biloba powder 10 to 30 % and Maritime pine powder 10 to 30 %.

The mixture may be formulated with pharmaceutically acceptable carriers such as di- or tricalcium phosphate and/or silicon dioxide.

The preferred embodiment according to the invention comprises a mixture of flavonoids derivable from these natural sources, such as onion powder, green

tea extract, apple powder, grape powder, Ginko Biloba powder and Maritime pine powder. The beneficial flavonoids are mainly quercetin and its derivatives, epigallocatechin-3-gallate and myricetin. It has been found that green tea extract can be provided with a very high level of epigallocatechin-3-gallate which has been found to have a beneficial effect on serious disorders such as cancer. Thus, epigallocatechin-3-gallate has an ability to inhibit the growth of cancer cells and it has been shown to reduce the size of malignant tumors. In combination with quercetin or its derivatives, the beneficial effect is enhanced. Myricetin has a similar effect.

It has been found that by combining powders and/or extracts of onion, green tea, apple, grape, Ginko Biloba and/or Maritime pine, naturally occurring flavonoids can be combined into a medicament which has the above beneficial effects in a surprisingly effective combination. The flavonoids in question are soluble in water at 35°C, i.e. at the human body temperature which ensures that the beneficial effect is obtained in the body.

When these naturally occurring flavonoid sources are combined with Vitamin C, the result is a medicament which has a good storage capacity and a surprisingly active therapeutic, prophylactic and palliative effect as deseribed above.

It has been known for long that green tea contains beneficial flavonoids. However, tests made in connection with the present invention show that the amount of epigallocatechin gallate in normal green tea is negligibly small. However, when green tea extract according to the present invention is used the epigallocatechin gallate levels rise to high proportions thus creating the active beneficial flavonoid ingredient of the present invention. Green tea extract which is enriched in epigallocatechin gallate is commercially available and is suitable for use in the present invention.

The flavonoid components may be present in the drug in the form of powders, liquids and/or extracts. The flavonoid components may be crystallized or concentrated.

A daily dosage of the flavonoid drug will depend on the formulation and- the disease in question. However, the flavonoid drug is non-toxic and based on naturally occurring sources. Therefore overdosing is hardly likely to occur.

The persons skilled in the art will realize that there exist a huge number of ways in which the flavonoid drug can be administered and the present invention should not be considered limited to the examples listed in the present specification.

The beneficial effect of the drug according to the invention on health is based on the flavonoids, especially a combination of flavonoids from apple, onion, green tea, grape, Ginko Biloba and/or Maritime pine, which the product contains. In the preferred drug composition the natural protective agents are in the right proportion to each other and are combined, with Vitamin C to prevent oxidation.

It will be obvious to persons skilled in the art that the proportions of the flavonoids may be varied according to the needs of the users. The drug according to the invention may also contain other components, such as further flavonoids, vitamins, and pharmaceutically acceptable carriers.

The drug according to the invention may be mixed with pharmaceutically acceptable carrier or filler compounds which are easily powdered and which add body to the drug. Such carriers are preferably inert compounds such as calcium phosphate and/or silica. The drug may he provided in a capsule or be produced in powder, tablet, liquid or cream form.

One aim of the present invention is also to provide a method for the reduction or prevention of the undesired oxidation of human cholesterol and/or DNA, in which the composition containing an effective amount of at least one flavonoid as the active ingredient is given to the person to be treated. Preferably said composition contains at least two, perferably three, flovonoids selected from the flavoinoids of onion, green tea, apple, grape, Ginko Biloba and Maritime pine.

In a especially preferred embodiment of method for reducing or preventing the oxidation of cholesterol and DNA in humans said flavonoids contained in the composition are selected from querectin and its derivatives, epigallocatechin-3-gallate and/or myricetin. Perferred amounts are: quercetin and/or its derivatives 10 to 30 mg/100 g and epigallochatechin-3-gallate 80 to 200 mg/100 g calculated on the weight of the product.

The invention will now be illustrated with the aid of a non-limiting example.

Example 1

Medical capsules were produced by encapsulating procedures well known in the art. In Table I below the composition of a capsule according to the invention is revealed.

Table I

Each capsule contained:		
gelatine	60 mg	23.1 %
microcrystalline cellulose (E 460)	46 mg	
onion powder	45 mg	17.3 %
dicalcium phosphate (E 540)	46 mg	
tea extract	36 mg	13.8 %
apple powder	27 mg	10.4 %
ascorbic acid (E 300)	2 mg	
silicium oxide (E 551)	2 mg	
magnesium stearate	2 mg	

The capsule was tested for presence of flavonoids by HPLC after acid hydrolysis. The capsule according to the invention was compared with the flavonoid contents of Phytorome green tea extract and normal green tea extract (Natural Gunpowder). A 4-fold extracted normal green tea contained less than 1.0 mg epigallocatechin gallate per 100 g of product. The capsule of the present invention was produced from the Phytomore green tea extract and contained 3280 mg cpigaflocatechin gallate per 100 g of product.

In the Table II below A stands for a capsule of the present invention; B stands for Phytomore green tea extract M 4115; and C stands for 4-fold water extracted Natural Gunpowder Tea.

Table II

Flavonoids (mg/100g fresh weight*)	A	B	C
epigallocatechin	-	-	-
epigallocatechin gallate	4870	6100	-
(-) gallocatechin	2020		
(-) gallocatechin gallate	3280		
(-) epicatechin	-	176	-
epicataechin gallate	1080	77	-
(+) catechin	-	806	82
kaempferol	30	191.2	128.0
myricetin	30	180.0	104.1
quercetin	60	338.6	232.5

Flavonoids (mg/100g fresh weight*)	A	B	C
isovitexin	-	-	85.8
vitexin	-	-	91.6

* The limit of quantitation is 1.0 mg/100 g.

The Table II shows that the capsule of the present invention contains a large proprotion of beneficial flavonoids.

Example 2

Table III below reveals the composition of another "Flavomare" capsule and extract according to the invention.

Table III

	capsule		extract
	mg/100 gr	mg/capsule	
Flavanols:			
epigallocatechin	-	-	23300
epigallocatechin gallate	4097	8,19	750
(-) epicatechin	460	0,92	2860
epicataechin gallate	949	1,90	-
gallocatechin	1624	3,25	3060
(-) gallocatechin gallate	2844	5,69	137
(+) catechin			
(+ -) catechin	1346	2,69	-
catechin gallate	389	0,78	-
kaempferol	24,4	0,05	232
quercetin	56,4	0,11	440
myricetin	23,6	0,05	184

- = no detectable amounts

In the following **Examples 3** and **4** the effect of the "Flavomare" capsule according Example 2 to the invention has been studied concerning cholesterol and DNA oxidation.

Example 3

Experimental method

Human volunteers of both sexes (N = totally 7) were given Flavomare-capsules for 4 weeks. In order to investigate possible dose-dependence of the effect, the Flavomare dose was increased in the middle of the Flavomare dosing period. During the first phase (the first 2-weeks dosing period) each participant

received 2 capsules/day; during the second phase (the last 2 weeks of dosing) the participants received 4 capsules/day.

Blood samples were taken four times: before start (1st time point = 0 week), in the middle (2nd time point = 2 week) and at the end of the Flavomare-period (3rd time point = 4 week), and after a 2 weeks recovery (4th time point = 6 weeks). In blood samples the following analyses were made:

* oxidized LDL (LDL baseline diene conjugation)
* LDL antioxidant potential (LDL-TRAP)
* serum total cholesterol
* serum LDL cholesterol
* serum HDL cholesterol

Analytical methods

Measurement of oxidized LDL (LDL baseline diene conjugation) was based on spectrophotometric determination of conjugated dienes in lipids extracted from LDL. Determination of LDL antioxidant potential (LDL-TRAP) was based on luminometric measurement of the ability of LDL sample to resist chemically-induced lipid peroxidation. Serum total, LDL and HDL cholesterol were assayed by commercial kits (Boehringer-Mannheim).

Results

Results are shown in Tables IV -VI. Flavomare was found to decrease the level of circulating oxidized LDL among participants of the study. Moreover, Flavomare doe-dependently decreased the ratio of oxidized LDL to LDL cholesterol. A slight increase was seen in LDL antioxidant potential, while the amounts of serum total, LDL and HDL cholesterol were not changed.

Table IV

The effect of Flavomare on LDL oxidation. LDL oxidation was measured by the baseline diene conjugation method (LDL-BDC). Results are given as the amount of oxidized LDL (µmol/mmol LDL cholesterol). Mean ± SD from 7 subjects.

	Oxidized LDL	Oxidized LDL / LDL cholesterol
1st time point	35.3 ± 4.3	11.4 ± 1.4
2nd time point	35.3 ± 5.2	10.9 ± 1.4
3rd time point	32.1 ± 3.2	10.0 ± 1.2
4th time point	37.7 ± 7.7	11.2 ± 1.3

Table V

The effect of Flavomare on LDL antioxidant potential (LDL-TRAP). LDL antioxidant potential was determined by the ability of the LDL sample to resist poroxyl radical-initiated lipid peroxidation. The results are given as µmol/mmol LDL cholesterol. Mean ± SD from 7 subjects.

	LDL-TRAP
1st time point	22.3 ± 1.6
2nd time point	23.0 ± 2.5
3rd time point	23.5 ± 3.2
4th time point	21.8 ± 2.9

Table VI

The effect of Flavomare on resum total, LDL and HDL cholesterol. The results are given as mmol/ L. Mean ± SD from 7 subjects.

	Total cholesterol	LDL cholesterol	HDL cholesterol
1st time point	5.34 ± 0.74	3.14 ± 0.42	1.14 ± 0.24
2nd time point	5.57 ± 0.65	3.21 ± 0.27	1.23 ± 0.15
3rd time point	5.40 ± 0.74	3.13 ± 0.51	1.15 ± 0.19
4th time point	5.62 ± 0.73	3.43 ± 0.44	1.26 ± 0.22

This result seems to indicate that Flavomare (i) can act as an antioxidant in human body and (ii) prevents LDL oxidation in vivo.

Example 4

Study Effect of Flavomare® on oxidation of human DNA in vivo

Background DNA oxidation is mutagenic and a major contributor to human cancer (Beckman & Ames. J. Biol Chem 272:19633-6, 1997). Therefore, factors, which protect DNA from oxidation, may decrease the risk of cancer.

Experimental design

Human volunteers of both sexes (n = 2) were given Flavomare-capsules (2 capsules / day) for 2 weeks. Blood samples were taken two times: Before start (1st time point = 0 week) and at the end of the Flavomare-period (2nd time point). DNA was isolated in whole blood samples and, as an indicator of oxidative DNA damage, the amount of 8-oxo-deoxyguanosine was determined by HPLC as described (Shihenaga et al., Methods Enzymol 234: 16-33, 1994).

Results

	1st time point	2nd time point
Subject 1	0.17	0.14
Subject 2	0.37	0.22

Results of the (pilot) study showed that suing Flavomare-capsules decreased the oxidation of human DNA.

Claims

1. A medicament and a dosage form and food additive for the therapeutic, prophylactic and/or palliative treatment of cancer, psoriasis, diabetes, rheumatism, cardiovaseular diseases, elevated blood pressure, elevated cholesterol levels, caries, colds, and stress, which comprises a composition containing at least one flavonoid as the active ingredient.

2. A composition used as medicament, dosage form and food additive for the protection and control of cholesterol and human DNA, RNA, lipids, enzymes, hormones in order to reduce and/or prevent the undesired oxidation thereof and as an antibiotic or cosmetic preparation which composition contains at least one flavonoid as the active ingredient.

3. The product according to claim 1 or 2, c h a r a c t e r i z e d in that said composition comprises a mixturc of at least two, and preferably three flavonoids in an orally, parenterally or topically administrable dosage form.

4. The product according to any of claim 1 to 3, c h a r a e t e r i z e d in that said flavonoid(s) is(are) selected from flavonoids of onion, green and/or black tea, and apple, grape, bark of Ginko Biloba and Maritime pine.

5. The product according to any one of claims 1 to 4, c h a r a c t e r i z e d in that.said composition contains an antioxidant, such as C-vitamin and/or E-vitamin.

6. The product according to any one of claims 1 to 5, c h a r a c t e r i z e d in that said flavonoid of green tea is an epigallocatehin gallate enriched extract of green tea.

7. The product according to any one of claims 1 to 6, c h a r a c t e r i z e d in that said flavonoids are derived from onion, green and/or black tea and apple as follows:

onion powder 35 to 50 %
tea extract 30 to 40 %
apple powder 20 to 30 %

8. The product according to any one of claims 1 to 7, characterized in that said flavonoids are derived from onion, green tea, apple, grape, the bark of Ginko Biloba and Maritime pine as follows:
onion powder 20 to 50 %
tea extract 10 to 40 %
apple powder 10 to 30 %
grape powder 10 to 40 %
Ginko Biloba bark powder 10 to 30 %
Maritime pine bark powder 10 to 30 %.

9. The product according to any one of claims 1 to 8, characterized in that said flavonoids are selected from querectin and its derivatives, epigallocatechin-3-gallate and myricetin.

10. The product according to claim 9, characterized in that said flavonoid contains quercetin and/or its derivatives in an amount of 10 to 30 mg/100 g and epigallochatechin-3-gallate 80 to 200 mg/100 g calculated on the weight of the product.

11. A dosage form for the therapeutic, prophylactic and/or palliative treatment of cancer, characterized in that said dosage form is a capsule, pill, tablet, cream, ointinent, liquid or an injectable fluid which contains at least one flavonoid as the active ingredient.

12. The dosage form according to claim 11, characterized in it contains a mixture of at least two, and preferably three flavonoids selected from flavonoids of onion, green and/or black tea, and apple.

13. The dosage form according to claim 12, characterized in that the the flavonoids additionally may be selected from flavonoids of grape, bark of Ginko Biloba and Maritime pine.

14. The dosage form according to 11, 12 or 13, characterizcd in that said flavonoids are selected from querectin and its derivatives, epigallocatechin-3-gallate and myricetin.

15. The dosage form according to any one of claims 11 to 14, characteri zed in that said composition contains an antioxidant, such as C-vitamin and/or E-vitamin.

16. The dosage form according to any one of claims 11 to 15. characteri zed in that said flavonoid of tea is provided in the form of an extract of green and/or black tea.

17. The dosage form according to claim 16, characterized in that said dosage form is a capsule containing

gelatine	60 mg	23.1 %
microcrystalline cellulose (E 460)	46 mg	
onion powder	45 mg	17.3 %
dicalcium phosphate (E 540)	46 mg	
green tea extract	36 mg	13.8 %
apple powder	27 mg	10.4 %
ascorbic acid (E 300)	2 mg	
silicium oxide (E 551)	2 mg	
magnesium stearate	2 mg	

18. The use of a flavonoid in the manufacture of a medicament for the therapeutic, prophylactic and/or palliative treatment of cancer.

19. The use according to claim 18, characterized in that said flavonoid is at least one flavonoid of onion, green and/or black tea, apple, grape, Ginko Biloba and Maritime pine.

20. The use according to claims 18 or 19, c h a r a c t e r i z e d in that said flavonoid of tea is provided by an epigallocatechin gallate enriched extract of green tea.

21. The use according to claim 19 or 20, c h a r a c t e r i z e d in that said flavonoids are selected from quercetin and its derivatives, epigallocatechin-3-gallate and myricetin.

22. A process for the preparation of a therapeutic, prophylactic and/or palliative medicament for cancer, c h a r a c t e r i z e d in that a powder and/or extract of onion, green tea, black tea, apple, grape, bark of Ginko Biloba and/or Maritime pine are mixed with at least one pharmaceutically acceptable carrier and formulated into a dosage form for oral, parenterai or topical administration.

23. A process according to claim 22, c h a r a c t e r i z e d in that a powder and/or extract of onion, green tea, apple are mixed with at least one pharmaceutically acceptable carrier and formulated into a dosage form for oral, parenterai or topical administration

24. The process according to claim 22 or 23, c h a r a c t e r i z e d in that an antioxidant, such as C-vitamin and/or E-vitamin is inciuded in the formulation.

25. A process for reduction or prevention of the undesired oxidation of human cholesterol and/or DNA, c h a r a c t e r i z e d in that a composition containing an effective amount of at least one flavonoide as the active ingredient is given to the person to be treated.

26. A process according to claim 25, c h a r a c t e r i z e d in that said composition contains at least two, perferably three, flovonoids selected from the flavoinoids of onion, green tea, apple, grape, bark of Ginko Biloba and Maritime pine.

27. A process according to claim 26, c h a r a c t e r i z e d in that said flavonoids are selected from querectin and its derivatives, epigallocatechin-3-gallate and/or myricetin

28. A process according to claim 27, c h a r a c t e r i z e d in that said flavonoids contain quercetin and/or its derivatives in an amount of 10 to 30 mg/100 g and epigallochatechin-3-gallate 80 to 200 mg/100 g calculated on the weight of the product.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 01/00001

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/353, A61K 35/78, A23L 1/29, A61K 7/00, A61P 39/06, A61P 43/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	STN International, File PROMT, PROMT accession no. 2000:351536, Marketing Intelligence Service Ltd.: "Cocktail Pyorykka Flavomare Meatballs MANUFACTURER: Elintarvike Selako CATEGORY: 040 - Meat.(International Pages)(Brief Article) (Product Announcement)"; & International Product Alert, (17 Apr 2000) Vol. 17, No. 8. ISSN: 1086-1238	1-17
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X	STN International, File EUMAS, EUMAS accession no. 493239, SLK FOUNDATION: "Flavomare", 19990412	1-17
	--	

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 April 2001	18 -04- 2001
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Gerd Strandell/EÖ Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 01/00001

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FR 2651132 A1 (PACIFIC CHEMICAL CO., LTD.), 1 March 1991 (01.03.91), the claims; page 9 - page 10	1-28
	--	
X	WO 9922728 A1 (ARCH DEVELOPMENT CORPORATION), 14 May 1999 (14.05.99), page 5, line 10 - page 6, line 29; page 7, line 14 - line 21; page 20 - page 21; figures 1, 5, 6; page 1, line 11 - line 14; the abstract	1-28
	--	
X	EP 0415126 A1 (MITSUI NORIN CO., LTD.), 6 March 1991 (06.03.91), page 1, line 1 - page 2, line 28	1,2,4,9,11, 14,16
	--	
X	EP 0443090 A2 (MITSUI NORIN CO., LTD.), 28 August 1991 (28.08.91), page 1, line 1 - page 2, line 44; the claims	1,2,4,9,11, 14,16
	--	
X	EP 0938897 A1 (JAPANESE FOUNDATION FOR CANCER RESEARCH ET AL), 1 Sept 1999 (01.09.99), page 3, line 20 - page 4, line 29; the claims	1,2,4,5,9, 11,14-16,18, 19,21-24
	--	
X	DE 4432549 A1 (HUR, KYE SUNG), 16 March 1995 (16.03.95), the claims; page 1, line 1 - page 4, line 33; the abstract	1,2,4,5,9, 11,14-16
	--	
X	Patent Abstracts of Japan, abstract of JP 7-223941 A (NIPPON HAM KK), 22 August 1995 (22.08.95)	1-3,9,11,14
	--	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 01/00001

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JP 60114153 A (OSAKA YAKUHIN KENKYUSHO KK) 1985-06-20 (abstract) World Patents Index (online). London, U.K.: Derwent Publications, Ltd. (retrieved on 2001-04-17). Retrieved from: EPO WPI Database. DW198531, Accession no. 1985-186600	1,2,4,11,16, 25,26
X	Patent Abstracts of Japan, abstract of JP 9-176010 A (KUREHA CHEM IND CO LTD), 8 July 1997 (08.07.97)	1,2,9,11,14
X	STNInternational, File CAPLUS, CAPLUS accession no. 1995:890867,Document no. 124:7638, Vinson, Joe A. et al: "Plant Flavonoids, Especially Tea Flavonols, Are Powerful Antioxidants Using an in Vitro Oxidation Model for Heart Disease"; & J. Agric. Food Chem. (1995), 43(11), 2800-2	1-2,4,9,11, 14,16,25-27
A	WO 9918811 A1 (OY ITARA H.K. AB), 22 April 1999 (22.04.99), claims 6, 7; page 3, fourth paragraph; page 2, first paragraph, last paragraph	1-28
A	WO 9818348 A1 (OY ITARA HK AB), 7 May 1998 (07.05.98), claims 7-9; page 2, last paragraph; page 3; page 5	1-28
A	US 5879733 A (ATHULA EKANAYAKE ET AL), 9 March 1999 (09.03.99), column 3, line 39 - line 41; column 10, line 18 - line 40	1-28

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI01/00001

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 25-28
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Claims 25-28 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT
Information on patent family members

25/02/01

International application No.
PCT/FI 01/00001

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR 2651132 A1	01/03/91	JP 2063369 C	24/06/96
		JP 3093782 A	18/04/91
		JP 7103025 B	08/11/95
		KR 9203062 Y	21/05/92
		KR 9707186 B	07/05/97
		KR 9109342 Y	07/12/91
WO 9922728 A1	14/05/99	AU 1289899 A	24/05/99
		EP 1027045 A	16/08/00
EP 0415126 A1	06/03/91	SE 0415126 T3	
		AT 117891 T	15/02/95
		DE 69016532 D,T	01/06/95
		JP 2975380 B	10/11/99
		JP 3086814 A	11/04/91
		US 5204089 A	20/04/93
EP 0443090 A2	28/08/91	AT 132753 T	15/01/96
		AU 628645 B	17/09/92
		AU 6239790 A	29/08/91
		CA 2025113 A	24/08/91
		DE 69024784 D,T	15/05/96
		JP 3005012 B	31/01/00
		JP 3246227 A	01/11/91
		US 5358713 A	25/10/94
EP 0938897 A1	01/09/99	CN 1226423 A	25/08/99
		JP 11246402 A	14/09/99
DE 4432549 A1	16/03/95	CN 1107355 A	30/08/95
		FR 2709965 A	24/03/95
		JP 7258103 A	09/10/95
		KR 9602892 Y	09/04/96
		KR 9711555 B	12/07/97
WO 9918811 A1	22/04/99	AU 9443898 A	03/05/99
		EP 1032279 A	06/09/00
		FI 973929 A	11/04/99
		NO 20001835 A	05/06/00
WO 9818348 A1	07/05/98	AU 1446597 A	22/05/98
		EP 0979040 A	16/02/00
		NO 992119 A	30/04/99
US 5879733 A	09/03/99	AU 1972997 A	10/09/97
		BR 9707675 A	13/04/99
		CA 2248295 A	28/08/97
		CN 1214613 A	21/04/99
		EP 0884953 A	23/12/98
		JP 11504224 T	20/04/99
		US 6063428 A	16/05/00
		WO 9730597 A	28/08/97